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ORIGINAL RESEARCH

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Overall and cancer specific survival following radical or adjuvant (chemo)radiotherapy in a retrospective cohort of elderly patients with endometrial cancer

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Abstract

To report the overall survival and cancer specific survival outcomes of elderly women aged ≥70 years who received radical or adjuvant (chemo)radiotherapy for endometrial cancer, we conducted a retrospective review of 93 patients from the West of Scotland Cancer Network (WoSCAN) who received pelvic (+/− para-aortic) radiotherapy over a 5-year period (January 2011 to December 2015, inclusive). Association of treatment type and other variables with overall survival (OS) and cancer specific survival (CSS) were analysed using log rank tests and Cox proportional hazards models. Median age of the study population was 74 years (range 70–90 years); over 50% of patients were aged ≥75 years, and over 25% were ≥80 years. The majority of patients had endometrioid endometrial cancer (75.3%), and 24.7% had a high-risk histological subtype. Stage distribution was as follows: I/II (40.9%); III/IV (41.9%); recurrent disease (17.2%). Radiotherapy was predominantly delivered in the adjuvant setting (61.3%); intent was primary (22.6%) or salvage (16.1%) in the remaining patients. Chemotherapy was administered to almost 50% of the cohort, mainly in conjunction with adjuvant radiotherapy. After median follow up of 96 months, 5-year OS and CSS were 50.5% and CSS 59.3% for the entire series, 57.9% and 62.8% in the adjuvant group, 23.8% and 35.7% in the primary group, and 60.0% and 80.0% in the salvage group, respectively. Age ≥80 years and primary radiotherapy were statistically significant predictors of poorer survival, adjusting for pathology, stage and grade (hazard ratio (HR) 2.06, 95% Confidence Interval (CI) (1.11–3.80), $p = 0.021$; and HR 2.42 (CI 1.28–4.57), $p = 0.006$ respectively). In summary, poorer OS was associated with use of (chemo)radiotherapy as primary treatment of endometrial cancer and/or in women aged ≥80 years, suggesting that careful risk/benefit analysis is required in these two groups.

Keywords

Endometrial cancer; Elderly; Radiotherapy; Chemotherapy; Chemoradiotherapy; Real-world; Surgery

1. Introduction

Endometrial cancer is largely a disease of older women and the incidence is increasing due to advancing age of the population [1]. Age is a significant prognostic factor and may be a consequence of late stage presentation and/or more aggressive biology. However, observational series suggest that the elderly are managed sub-optimally [2–5], leading to poorer outcomes. Standard treatment consists of surgery; total hysterectomy (TH) and bilateral salpingo-oophorectomy (BSO) +/− pelvic/para-aortic lymph node dissection, in addition to omentectomy in cases with non-endometrioid pathology. Tailored adjuvant therapy is then advised based on individual risk factors [6]. External beam radiotherapy to the pelvis, for example, is indicated for high-intermediate or high-risk disease to reduce pelvic recurrence. The role of adjuvant chemotherapy in stage I–III disease has long been a controversial topic, but the recent PORTEC-3 Phase III randomised trial signified that post-operative cisplatin-based chemoradiotherapy followed by 4 cycles of carboplatin/paclitaxel chemotherapy should be considered standard of care in stage III and/or high grade serous endometrial cancer [7, 8]. Historically, it was common practice to exclude patients aged ≥70 years from Phase III trials, but contemporary studies typically do not cap on age alone. In PORTEC-3, for instance, almost 20% of women were aged ≥70 years. This older subgroup with high-risk disease also derived a benefit from chemoradiotherapy compared with radiotherapy alone; 5-year overall survival (OS) was 76% with chemoradiotherapy versus 58% with radiotherapy, respectively [7]. It is uncertain whether

PORTEC-3 can be extrapolated to the "real-world" elderly population and if the advantage applies to even older women, ≥80 years.

In women who are not fit for surgery, regardless of age, primary radiotherapy is an option. Pelvic control rate is excellent for early stage endometrial cancer but 5-year OS varies widely from 30–95% [9–17]. In studies that have compared OS with cancer specific survival (CSS), the latter is often markedly higher [16, 17], indicating that many patients succumb to underlying medical conditions. An aggressive course of therapy is futile if there is a high probability of death from an unrelated illness or if treatment itself induces unacceptable morbidity (or mortality) due to poor tolerance. In the context of significant co-morbidities, careful assessment of the merits of radical radiotherapy versus palliative measures must be undertaken on an individual basis. At present, this is largely based on clinician judgement, but some centres have integrated care of the elderly multidisciplinary teams.

The West of Scotland Cancer Network (WoSCAN) serves almost 50% of the Scottish population; a significant proportion of whom are overweight. In addition, the prevalence of chronic medical conditions, particularly cardiovascular disease and diabetes mellitus, is high. To that end, we aimed to evaluate the OS and CSS outcomes of elderly women (≥70 years) who received adjuvant or radical (chemo)radiotherapy for endometrial cancer.

2. Methods

A retrospective observational study was performed; the target population comprised women ≥70 years with endometrial cancer who commenced radical or adjuvant radiotherapy to the pelvis within WoSCAN between January 2010 and December 2015. Patients were identified using the radiotherapy electronic prescribing and planning system. Women were followed up until death, or the end of the study period (31 December 2020).

2.1 Patient selection and treatment details

Patients were discussed at multidisciplinary tumour board meetings. Endometrial biopsy (or vaginal vault biopsy in the event of recurrence) was imperative. Imaging routinely consisted of computed tomography thorax/abdomen/pelvis. Surgery comprised TH and BSO as a minimum, plus omentectomy in non-endometrioid subtypes. Pelvic (+/− para-aortic) lymph node dissection was individualised based on radiological findings and medical co-morbidities/body mass index.

Adjuvant radiotherapy was delivered as follows: external beam radiation to the pelvis (or extended field)-45 Gy in 25 fractions. In cases with cervical stromal invasion, high dose rate vaginal cylinder brachytherapy was also prescribed (12 Gy in 3 fractions). If radical or salvage radiotherapy was the definitive treatment then external beam radiation was administered followed by brachytherapy (24 Gy in 4 fractions); either an intra-uterine ring and tandem, or colpostats. Prior to 2014, external beam was planned conformally with a 4-field brick set-up. Thereafter, treatment was delivered by volumetric arc therapy. Chemotherapy consisted of up to 6 cycles of 3-weekly carboplatin/paclitaxel (administered prior to radiotherapy) or weekly concurrent cisplatin (40 mg/m^2) for 5 weeks.

Follow up consisted of abdominal and pelvic examination on a 3–6 monthly basis until 5 years had elapsed, or death had occurred. Imaging was requested based on symptoms and clinical signs.

2.2 Data sources

Data were collected from information stored in radiotherapy and chemotherapy management systems, and Clinical Portal, an electronic application providing socio-demographic information and details on treatment outcomes. Death records were obtained from the Acute, Cancer, Deaths and Mental Health system. Statistical analysis was performed using Stata® version 14 (StataCorp LLC, College Station, TX, USA).

2.3 Statistical analysis

Median OS and CSS along with 95% Confidence Intervals (CI)—were estimated using Kaplan-Meier (KM) methodology. Median follow up was estimated using the reverse KM method. For OS and CSS, 31 December 2020, served as censor date for those still alive at study end. Log-rank tests were used to identify differences in survival by baseline characteristics. Cox proportional-hazard models were used to estimate unadjusted hazard ratios for survival, for the following variables: age group, performance status, pathology, stage, grade, number of co-morbidities, treated with chemotherapy, and radiotherapy for inoperable disease. Multivariable models included age group, pathology, stage, grade, and radiotherapy for inoperable disease. The proportional hazard assumption was assessed using Schoenfeld residuals.

3. Results

3.1 Baseline characteristics

A total of 93 patients were identified. The median age was 74 years. Over 50% were aged ≥75 years and 28% were ≥80 years. At least two co-morbidities were recorded in 56% of women. Stage distribution was as follows; stage I/II (40.9%), stage III/IV (41.9%), recurrent pelvic disease (17.2%). Pathological subtype consisted of endometrioid (75.2%), high grade serous (10.8%), or other (14.0%); predominantly carcinosarcoma. The majority of women (61.3%) had radiotherapy with adjuvant intent. Radiotherapy was the definitive mode of treatment in 37 (38.4%) women. Of these, 22 were considered inoperable on medical grounds. The remaining15 patients had salvage radiotherapy (in the context of previous TH and BSO for endometrial cancer; vaginal relapse only (7/15), isolated pelvic mass (4/15), pelvic and/or para-aortic nodal recurrence +/− vaginal involvement (4/15). Median follow up time was 96 months (inter quartile range (IQR) 75 to 108 months). Table 1 shows the baseline characteristics.

TABLE 1. Baseline characteristics.

Characteristic	Variable	Number n (%)
Age		
	Median 74 years	
	Range 70–90 years	
Age distribution		
	70–74 years	46 (49.4%)
	75–79 years	21 (22.6%)
	≥80 years	26 (28.0%)
ECOG Performance Status		
	0–1	26 (28.0%)
	2–3	10 (10.8%)
	Unknown	57 (61.2%)
Pathology		
	Endometrioid	70 (75.2%)
	Carcinosarcoma/clear cell	13 (14.0%)
	Serous	10 (10.8%)
Stage (FIGO 2009)		
	I	27 (29.1%)
	II	11 (11.8%)
	III	31 (33.3%)
	IV	8 (8.6%)
	Recurrent	16 (17.2%)
Grade		
	1–2	41 (44.1%)
	3	48 (51.6%)
	Unknown	4 (4.3%)
Comorbidities		
	0–1	28 (30.1%)
	2–3	33 (35.4%)
	4 or more	18 (19.4%)
	Unknown	14 (15.1%)
Surgery		
	TH/BSO	44 (47.2%)
	TH/BSO + nodal staging	5 (5.4%)
	TH/BSO + omental staging	13 (14.0%)
	TH/BSO + nodal & omental staging	10 (10.8%)
	N/A	21 (22.6%)
Radiotherapy intent		
	Adjuvant	57 (61.3%)
	Primary (medically inoperable)	21 (22.6%)
	Salvage	15 (16.1%)

Abbreviations: ECOG—Eastern Cooperative Oncology Group; FIGO—International Federation of Gynaecology and Obstetrics; TH—total hysterectomy; BSO—bilateral salpingo-oophorectomy; N/A—not applicable.

3.2 Radiotherapy

External beam radiation was delivered to the pelvis in 86 women (92.5%); less than 10% received extended field. Median dose was 45 Gy in 25 fractions. A brachytherapy boost was prescribed in 47 women (50.5%). All planned radiotherapy was completed in 83 women (89.3%). Median time to complete treatment was 36 days. There were 5 deaths within 30 days of radiotherapy (none in the adjuvant cohort; 80% occurred in the ≥80 age group).

3.3 Chemotherapy

Of the 57 adjuvant patients, 36 received chemoradiotherapy (sequential 53%, concurrent 41%, both 6%) and 21 had radiotherapy alone. Median number of adjuvant and concurrent cycles were 4 (range 1–6) and 5 (range 3–6), respectively. A further 8 patients in the other 2 groups received chemotherapy (neoadjuvant intent with carboplatin/paclitaxel, or concomitant cisplatin). Additional information on age, stage, and pathology, in the adjuvant group is demonstrated in Table 2.

3.4 Survival

At study end, 50 (53.8%) patients had died (<80 years–32/67, ≥80 years–18/26) and 38/50 deaths were directly attributable to endometrial cancer (5/50 unknown). OS at 5-years for entire cohort was 50.5%, 95% CI (40.0–60.2%). Survival based on age, stage, treatment intent, and use of chemotherapy is illustrated in Fig. 1A–D, respectively. Median OS was poorer in women ≥80 years (23 months 95% CI (4.9–58.7)) compared with those aged 70–79 years (108 months) (p = 0.012). OS was also inferior in women receiving primary radiotherapy for inoperable disease (median 31.9 months, 95% CI (3.2–41.2), p = 0.013) but there is no observable difference whether chemotherapy was administered or not (p = 1.00). Age ≥80 and primary radiotherapy remained statistically significant predictors of poorer survival in multivariable Cox regression (Table 3) adjusting for pathology, stage and grade (HR 2.06, 95% CI (1.11–3.80), p = 0.021; and HR 2.42, 95% CI (1.28–4.57), p = 0.006, respectively).

Five-year OSS and CSS were 50.5% 95% CI (40.0 to 60.2%) and 59.3% 95% CI (48.4 to 68.6%) for the entire cohort (Fig. 2A–B). For the adjuvant group 5-year OS and CSS were 57.9% 95% CI (44.1–69.5%) and 62.8% (48.8–73.9%) respectively (Fig. 2C–D). For those who had received primary radiotherapy 5-year OS and CSS were 23.8% 95% CI (8.7–43.1%) and 35.7% (15.8–56.3%) (Fig. 2E–F). Among those who received salvage radiotherapy 5-year OS and CSS were 60.0% 95% CI (31.8–79.7%) and 80.0% (50.0–93.1%) (Fig. 2G–H).

4. Discussion

In a retrospective cohort of 93 endometrial cancer patients aged ≥70 years who received adjuvant or radical (chemo)radiotherapy, 5-year OS and CSS were 50.5% and 59.3%, respectively. Almost 25% had non-endometrioid pathology, and over 40% had at least stage III disease. Compliance rates with radiotherapy were high but 5 deaths

TABLE 2. Patient demographics of adjuvant cohort.

Characteristic	Variable	CRT n = 36	RT n = 21
Age			
	Median	73 years	74 years
	(Range)	(70–83 years)	(71–86 years)
Age distribution			
	<80 years	31 (86.1%)	15 (71.4%)
	≥80 years	5 (13.9%)	6 (28.6%)
ECOG Performance Status			
	0–1	5 (23.8%)	15 (41.7%)
	2–3	2 (9.5%)	1 (2.8%)
	Unknown	14 (66.7%)	20 (55.5%)
Pathology			
	Endometrioid	22 (61.1%)	18 (85.7%)
	Non-endometrioid	14 (38.9%)	3 (14.3%)
Stage (FIGO 2009)			
	I/II	10 (27.8%)	17 (81.0%)
	III/IV	26 (72.2%)	4 (19.0%)
Comorbidities			
	0–1	14 (38.9%)	6 (28.6%)
	2–3	13 (36.1%)	8 (38.1%)
	4 or more	5 (13.9%)	4 (19.0%)
	Unknown	4 (11.1%)	3 (14.3%)
Surgery			
	TH/BSO +/− omental staging	23 (63.9%)	20 (95.2%)
	TH/BSO + nodal staging	13 (36.1%)	1 (4.8%)

Abbreviations: CRT—chemoradiotherapy; RT—radiotherapy; IQR—Interquartile range; ECOG—Eastern Cooperative Oncology Group; FIGO—International Federation of Gynaecology and Obstetrics; TH—total hysterectomy; BSO—bilateral salpingo-oophorectomy.

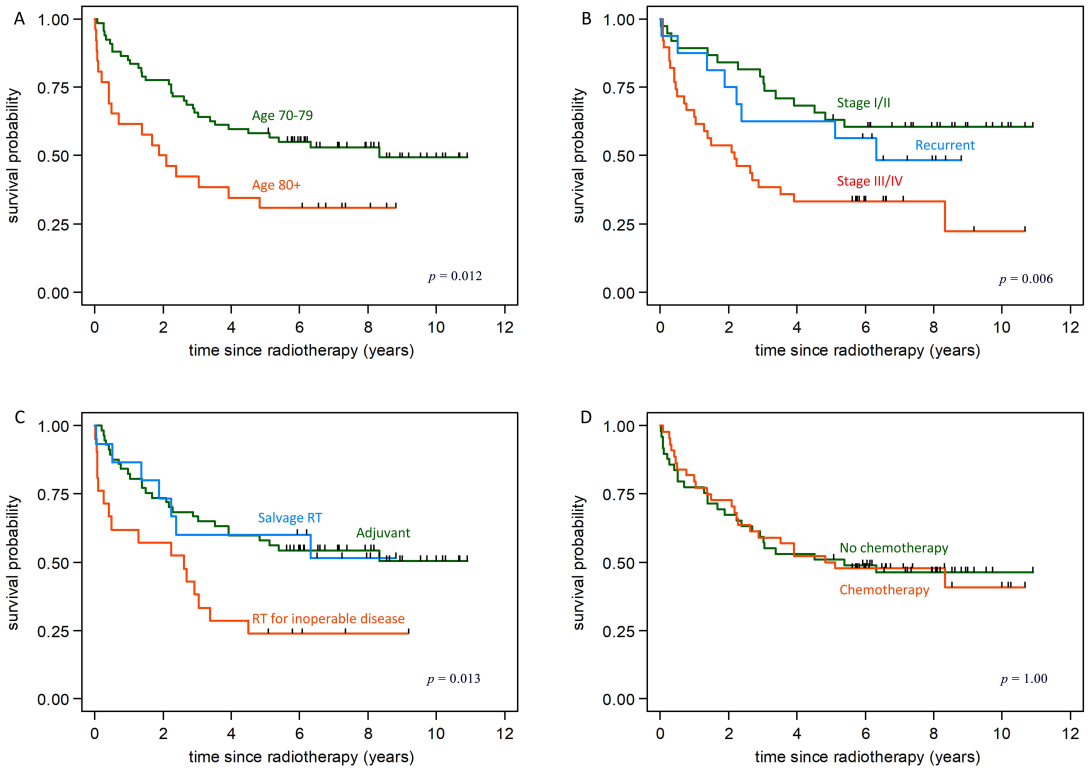

FIGURE 1. Overall survival (A—by age group, B—stage, C—treatment intent, D—chemotherapy).

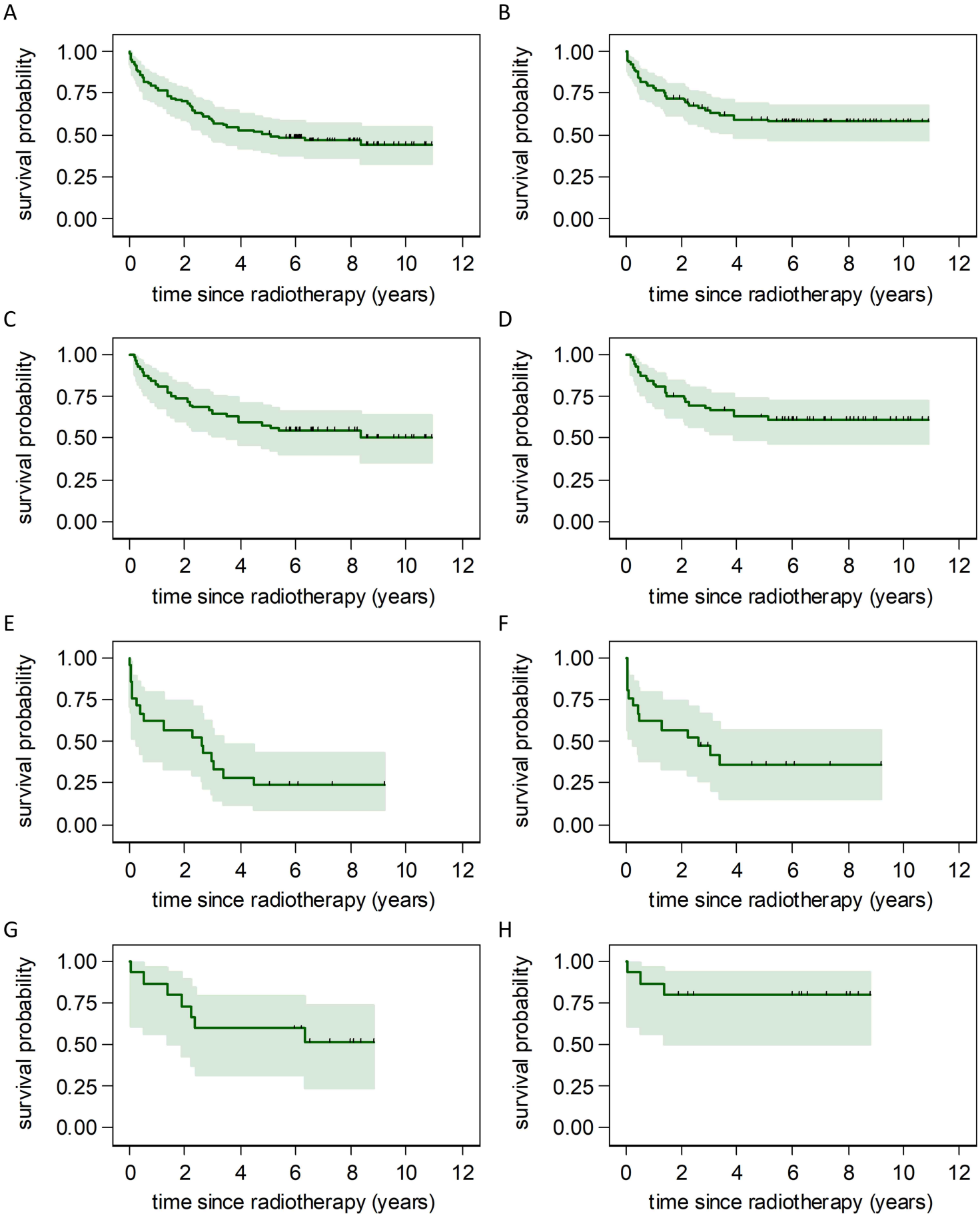

FIGURE 2. Overall and cancer specific survival (A & B—all, C & D—adjuvant, E & F—primary, G & H—salvage).

TABLE 3. Overall survival analysis by baseline characteristics & definitive therapy received.

				Univariate analysis				Multivariate		
Characteristic	N	Deaths	(%)	log rank test *p*-value	HR	95% CI	*p*	HR	95% CI	*p*
Age group										
70–79	67	32	47.8	0.012	1			1		
80+	27	18	66.7		2.06	(1.15–2.68)	0.014	2.06	(1.11–3.80)	0.021
Performance status										
0	11	5	45.5	0.495	1					
1	15	8	53.3		1.36	(0.44–4.15)	0.594			
2–3	10	7	70.0		2.26	(0.71–7.15)	0.166			
unknown	57	30	52.6		1.29	(0.50–3.34)	0.593			
Pathology										
Endometrioid	70	33	47.1	<0.001	1			1		
Non-endometrioid	23	17	73.9		2.64	(1.46–4.77)	0.001	1.83	(0.84–3.95)	0.126
Stage										
I, II	38	15	39.5	0.006	1			1		
III, IV	39	27	69.2		2.67	(1.41–5.05)	0.003	2.22	(1.12–4.40)	0.022
recurrent	16	8	50.0		1.42	(0.60–3.36)	0.425	1.87	(0.72–4.83)	0.199
Grade										
1–2	41	17	41.5	0.017*	1			1		
3	48	31	64.6		2.02	(1.12–3.65)	0.020	1.39	(0.66–2.90)	0.383
unknown	4	2	50.0		1.70	(0.39–7.39)	0.477	1.08	(0.23–5.07)	0.923
Comorbidity										
0–1	28	18	64.3	0.213	1					
2+	51	25	49.0		0.61	(0.33–1.11)	0.106			
unknown	14	7	50.0		0.57	(0.24–1.38)	0.215			
Chemotherapy										
No	49	26	53.1	1.000	1					
Yes	44	24	54.5		1.00	(0.57–1.74)	0.998			
Primary RT										
No	72	24	33.3	0.003	1			1		
Yes	21	16	76.2		2.40	(1.32–4.38)	0.007	2.42	(1.28–4.57)	0.006

Abbreviations: HR—hazard ratio; CI—confidence interval; RT—radiotherapy.
**Grade 3 versus grade 1–2.*

occurred within 30 days of completing treatment. OS is not influenced by chemotherapy but is compromised in women ≥80 years and in those who receive radiotherapy with radical intent where primary surgery is not an option.

Age is an acknowledged prognostic factor in endometrial cancer. The precise reason for poorer outcomes is likely multifactorial, encompassing adverse biology, suboptimal surgery and/or staging, and inequitable access to post-operative therapy [2–5]. PORTEC-3 clearly demonstrated that age need not be a barrier to adjuvant treatment, providing the patient is counselled regarding toxicity. The trial reported a 5-year OS rate of 67% for women ≥70 years, but more specifically, the survival benefit approached 20% across all age groups with the addition of chemotherapy to radiotherapy (5-year OS 76% with chemoradiotherapy compared with 58% in radiotherapy arm) [7, 8]. Our results indicated a slightly less favourable 5-year OS rate of 57.9% in the adjuvant cohort despite 63% of these women receiving chemotherapy, but we included very high-risk patients, including those with stage IV and/or residual disease, and aggressive pathology such as carcinosarcoma, all of whom would have been excluded from PORTEC-3. In addition, the proportion of patients who had nodal staging was lower (25% in WoSCAN versus 57% in PORTEC-3), again highlighting the potentially more advanced nature of our series. Performance status was not always documented, but at least 10% were recorded as performance status 2 in WoSCAN as

opposed to 2% in PORTEC-3 [7]. Hypertension was the most common medical condition in PORTEC3, recorded in 30–35% of study participants [7]. Co-morbidities were frequently reported in our population; at least 2 or more in >50% patients.

We acknowledge that there were differences in both the radiotherapy and chemoradiotherapy regimens. Standard radiotherapy protocol at our centre is 45 Gy in 25 fractions but PORTEC-3 utilised a higher dose of 48.6 Gy in 27 fractions (although 45 Gy in 25 fractions was permitted in 1/3 recruiting UK centres) [7]. This is unlikely to influence survival, but may affect pelvic control, especially as a sensitising dose of cisplatin was administered routinely in PORTEC-3 and radiotherapy was delivered first as opposed to our reverse sequencing (with the exception of those who received concurrent chemotherapy). However, we have not assessed site of recurrence. It is unclear whether scheduling and/or dose intensity is important in order to achieve optimal survival advantage. A fundamental concern in our patient cohort is the ability to tolerate 4 cycles of carboplatin/paclitaxel before or after pelvic radiotherapy. Indeed, this prompted the use of weekly cisplatin as an alternative regimen. Lower dose intensity may explain the lack of survival benefit in our series, but the similar OS in chemoradiotherapy and radiotherapy groups may be due to confounding factors.

Significantly, the patients in this series were all treated prior to publication of PORTEC-3, therefore the decision to prescribe chemotherapy was based on institutional practice/clinician preference. Chemoradiotherapy was more likely than radiotherapy to be administered to patients with stage III/IV endometrial cancer and non-endometrioid pathology, indicating that extent of disease and/or biology influenced choice of therapy. However, we cannot completely rule out selection bias as chemotherapy may have been offered to the fittest patients, although co-morbidity rates were analogous. Nonetheless, comparable 5-year OS and CSS in the adjuvant group indicates that endometrial cancer was the predominant cause of death, emphasizing the high-risk nature of this population and suggesting that patients are selected for adjuvant treatment appropriately on medical grounds. Accordingly, compliance rate with radiotherapy was excellent and there were no deaths during or up to 30 days afterwards.

Almost 40% of our series had definitive radical (chemo)radiotherapy, either primary or salvage therapy. The OS results for women receiving salvage treatment are comparable to other series [18–20]. Conversely, 5-year OS was poor, at just 23.8%, in the medically inoperable patients. Local institution protocol consists of standard pelvic radiotherapy followed by intra-uterine brachytherapy delivered over two procedures, requiring general or spinal anaesthetic. For women with stage 1A grade 1 or 2 endometrioid endometrial cancer, brachytherapy alone has been shown to produce excellent results [14, 21] and is an attractive alternative to a prolonged and potentially toxic course of combined treatment, especially if life expectancy is thought to be reduced. What is more, some institutions have developed protocols that utilise local anaesthetic/sedation only [22]. It is notable that all 5 deaths within 30 days of radiotherapy occurred in this group, 4/5 aged ≥80 years, suggesting poorer tolerance to pelvic radiotherapy in very elderly women. CSS was higher than OS in both groups, illustrating the contribution from medical conditions other than cancer and is not surprising, especially in the context of inoperability.

The main strength of this retrospective study is the long follow up period. External beam radiotherapy was consistent across all 3 groups, but patient selection for chemotherapy was subject to bias. In addition, adjuvant chemotherapy regimens diverged from the PORTEC-3 protocol. More in depth statistical analysis of the effect of treatment with chemotherapy and age was limited by the relatively small numbers per subgroup. Unfortunately, information on performance status and co-morbidities was not always available; both characteristics are particularly pertinent in an ageing population. Adverse event data was also not collated. Finally, radiotherapy planning and delivery became more sophisticated during the study period, but is unlikely to have had any effect on survival outcome.

Adjuvant chemoradiotherapy is an appropriate option for fit women ≥70 years with high-risk endometrial cancer based on the outcome of a randomised Phase III trial. Our findings illustrate that chemoradiotherapy is feasible in a "real-world" setting, but the precise additional benefit of chemotherapy is unclear. OS following primary (chemo)radiotherapy in elderly women with inoperable endometrial cancer, on medical grounds, is poor. Patient selection for (chemo)radiotherapy is important, most notably in women ≥80 years; emerging frailty scores and comprehensive geriatric assessment may be the key to optimising outcomes [23]. Ultimately, disease control must be carefully balanced with toxicity-related quality of life in the elderly population. De-escalation of treatment or alternative regimens are currently under investigation in other gynaecological cancers, notably ovary [24]. This may be more difficult to implement in endometrial cancer as hypofractionation of pelvic radiotherapy is not an attractive option. In the context of primary inoperable disease, brachytherapy alone appears to be a valid option for stage IA grade 1–2 endometrioid endometrial cancer and may supersede combined regimens [25, 26]. Perhaps, de-escalation of chemotherapy could be explored in more detail in the adjuvant setting; concurrent weekly cisplatin utilised in our series has the advantage of being a well-established regimen in cervical cancer [27] and significantly reduces overall treatment length. Finally, increased understanding and access to molecular stratification in endometrial cancer will re-define and shape the entire adjuvant treatment pathway [28–30].

5. Conclusions

In conclusion, radiotherapy compliance rate in this series was almost 90%, but age ≥80 years and (chemo)radiotherapy as primary mode of treatment had a detrimental impact on survival. Endometrial cancer remained the major cause of death despite high prevalence of co-morbidities. In the adjuvant group, OS is slightly less favourable than the PORTEC-3 data, but this is an unselected population, 20% of whom were aged ≥80 years, and a proportion had stage IV disease and/or aggressive pathology such as carcinosarcoma. Also, almost 40% of chemoradiotherapy consisted of weekly cisplatin as per

local protocol as opposed to the more intensive PORTEC-3 sequential regimen. (Chemo)radiotherapy is justified in elderly women (70–79 years) with high-risk/inoperable endometrial cancer, but careful selection is advised in women aged ≥80 years as the median survival in this group was less than 2 years.

AUTHOR CONTRIBUTIONS

CC, KF, KG, MC and PM—performed the data analysis. CC, KF, KG, PM—contributed to the interpretation of the results. KG—drafted the paper. All authors were involved in critically revising the text, and all authors read and approved the final version of the manuscript. All authors contributed to the study concept and design.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

As per local guidelines, formal ethics committee approval was not required for this work (study design: retrospective case series). All data were handled in compliance with Caldicott guidelines. No consent was required as no patient identifiable information was included.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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